REMARKS

Reconsideration of the above-identified application in view of the following remarks is respectfully requested.

Claims 1-9 are pending in this case. Claims 3 and 4 have been withdrawn from further consideration as being drawn to a non-elected invention. Claims 1, 2 and 7-9 have been examined on merits. Claims 1, 2 and 7-9 have been rejected. Claims 1, 2 and 5-9 have been objected to. Claims 1, 5 and 8 have now been amended.

The claims before the Examiner are directed towards peptides that are patterned after known GSK-3 substrates, which are subjected to a site-specific modification of the recognition motif of GSK-3. The present invention is based on the recognition that GSK-3 has a very unique recognition motif and that therefore the binding of this enzyme to substrates is highly specific.

Thus, more specifically, the peptide inhibitors disclosed by the present invention have an amino acids sequence that is a part of a known GSK-3 substrate and in which that part of the sequence that serves as the GSK-3 recognition motif (namely, a unique amino acids sequence in the substrate which is recognized only by this enzyme) has been site-specifically modified such that the recognition and binding of the GSK-3 to the peptide are maintained (similarly to those in a GSK-3 substrates), while the activity of the GSK-3 (namely, phosphorylation and autophosphorylation) is inhibited.

As is demonstrated in the Examples section of the instant application (see, for example, Exampels 1 and 2), during experimentation, a few parameters that are required both for the recognition and binding of a peptide to GSK-3 and for inhibiting the activity of GSK-3 have been determined. Thus, it has been shown, for example, that peptides that do not have a phosphorylated serine residue do not bind to GSK-3 and thus cannot serve neither as substrates nor as inhibitors of GSK-3; and that a serine residue at the fourth position upstream the phosphorylated serine residue is required for the activity of GSK-3. It was therefore concluded that a site-specific modification, as discussed hereinabove, should be effected on this serine residue, while maintaining all other features of the GSK-3 substrate.

The prior art fails to teach such peptides which are specifically designed so as to bind to and be recognized by GSK-3, by being patterned after a known GSK-3 substrate.

Priority

The Examiner has stated that the claim for priority set forth in paragraph [0001] of the specification is objected to because of an incorrect asserted relationship between this application and parent application serial No. 09/951,902. The Examiner's objection is respectfully traversed. Claims 1 and 5 have been amended.

Specifically, the Examiner has stated that the instant application discloses subject matter in addition to the subject matter disclosed in the parent application, namely, peptide inhibitors comprising an amino acid sequence which is part of a natural substrate of GSK-3, whereby the original disclosure in the parent application does not disclose natural substrates of GSK-3 in general, and does not disclose GSK-3 inhibitors which are derived from natural substrates of GSK-3 in general. The Examiner has continued stating that because the instant application discloses subject matter in addition to that disclosed in the parent application, the claim for priority should be amended to recite that this application is a continuation-in-part rather than a divisional of parent application serial No. 09/951,902.

Applicant wishes to point out in this respect that in parent application serial No. 09/951,902, GSK-3 peptide inhibitors patterned after a known GSK-3 substrate are taught throughout (see, for example, paragraphs [0031]). Moreover, in paragraph [0033] and in the Examples section of parent application serial No. 09/951,902 (see, for example, Examples 1 and 2), the preparation and inhibitory activity of peptides patterned after two known substrates of GSK-3, CREB (cAMP response element binding protein) and heat shock-factor-1 (HSF-1), is discussed and demonstrated.

Applicant wishes to further point out that it should be well understood that the phrase "a known GSK-3 substrate", cited throughout parent application serial No. 09/951,902, means, or at least encompasses, natural GSK-3 substrates. Such an interpretation is further clarified by the fact that the rationale behind the design and preparation of the peptide inhibitors taught in the instant application is based on

amino acid sequences of known GSK-3 substrates and as such, it would be clear that natural GSK-3 substrates should optimally serve this purpose of the present invention. In addition, this interpretation is further clarified by the fact that an experimentation was conducted with peptide inhibitors that are derived from natural GSK-3 substrates (the CREB and HSF-1 cited *supra*).

Applicant therefore believes that by disclosing "known GSK-3 substrates" the parent application also discloses "natural GSK-3 substrates" and hence that the instant application does not present an additional subject matter thereto.

Notwithstanding the above, and in order to overcome the Examiner's objections, Applicant has chosen to amend claim 1 so as to no longer recite the controversial phrase "a natural substrate of GSK-3" and to recite instead "a known GSK-3 substrate". Accordingly, claim 5 has also been amended to recite "said known substrate of GSK-3" instead of "said natural substrate of GSK-3".

Applicant believes that upon this amendment, the instant application does not disclose an added subject matter to that disclosed in the parent application serial No. 09/951,902, and hence that the claim for priority set forth in paragraph [0001] of the specification is correctly presented.

Applicant therefore believes to have overcome the Examiner's objection in this respect.

Specification

The Examiner has objected to the specification as failing to provide proper antecedent basis for the claimed subject matter, since the specification does not recite peptide inhibitors that comprise an amino acid sequence that is part of a natural substrate of GSK-3 (as cited in claim 1). The Examiner's objection is respectfully traversed. Claims 1 and 5 have been amended.

Specifically, claim 1 has now been amended to no longer recite the controversial phrase "a natural substrate of GSK-3" and to recite instead "a known GSK-3 substrate". Hence, amended claim 1 recites a peptide inhibitor that comprises an amino acid sequence that is a part of a known GSK-3 substrate. As is argued hereinabove, such a peptide inhibitor is widely described in the specification of both

the parent application and the instant application (see, for example, the summary section and paragraphs [0030]-[0037]).

Accordingly, claim 5 has been amended to no longer recite the controversial phrase "said natural substrate of GSK-3" and to recite instead "said known substrate of GSK-3".

It is therefore the Applicant's opinion that the specification provides proper antecedent basis for the subject matter as claimed in amended claim 1, claim 2, amended claim 5 and claims 6-9.

Applicant therefore believes to have overcome the Examiner's objection in this respect.

Claims objection

The Examiner has stated that claims 1, 2 and 7-9 are objected to because in claim 1 the phrase "to inhibit" should be re-written as "of inhibiting".

Claim 1 has been amended accordingly, to thereby overcome the Examiner's objection.

35 U.S.C. § 112, Second Paragraph Rejections

In one particular, the Examiner has rejected claims 1, 2 and 7-9 as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. Claims 1 and 8 have been amended.

More specifically, the Examiner has stated that at claim 1, the phrase "a natural substrate of GSK-3 substrate" is unclear and has suggested deleting the word "substrate" occurring after "GSK-3".

Claim 1 has been amended to longer recite the phrase "a natural substrate of GSK-3 substrate" and to recite instead the phrase "of a known GSK-3 substrate".

In another particular, the Examiner has stated that the meaning of claim 8 is unclear.

Claim 8 has been amended to recite that *"..., an amino acid residue at the position three residues upstream of Z is an amino acid residue other than a glutamic acid residue".*

The Examiner's attention is directed in this respect, for example, to paragraphs [0030]-[0037] of the instant application, where the concept and rationale of the present invention is set forth. In brief, in these paragraphs, the concept of GSK-3 peptide inhibitors which are derived from known GSK-3 substrates is described. In general, these peptide inhibitors are designed to have the recognition motif of a GSK-3 substrate, whereby a serine residue is replaced by any other amino acid residue. As is specifically cited in paragraph [0037], in cases where a GSK-3 substrate has a glutamic acid residue three residues upstream of the first serine residue of the recognition motif, replacing this glutamic acid residue results in improved inhibitory activity of the peptide.

It is therefore clear the original wording of claim 8 was meant to present the preferred embodiment described in paragraph [0037] and hence to recite that when a GSK-3 substrate of which the "modified" recognition motif is part of, originally includes a glutamic acid residue at a certain position, in the peptide inhibitor that is derived from this substrate, this residue is replaced by any amino acid residue other than glutamic acid.

However, in order to more clearly define the subject matter claimed in claim 8, claim 8 has been amended so as to recite that at a certain position of the peptide inhibitor, the amino acid residue is other than glycine. Applicant believes that the features of the claimed peptide inhibitor in this respect are now clearly defined.

Applicant therefore believes to have overcome the Examiner's rejections.

35 U.S.C. § 102(b) rejections

In one particular, the Examiner has stated that the effective filing date of claims 1, 2 and 7-9 is deemed to be the filing date of the instant application (March 29, 2004). Specifically, the Examiner has stated that claims 1, 2 and 7-9 are not deemed to be entitled under 35 U.S.C. 120 to the benefit of the filing date of parent application serial No. 09/951,902 because the patent application does not disclose peptide inhibitors comprising an amino acid sequence which is part of a natural substrate of GSK-3. The Examiner has continued stating that accordingly, the WO

Patent Application 01/49709, is available as prior art under 35 U.S.C. § 102(b) against claims 1, 2 and 7-9.

Claim 1 has been amended to no longer recite the phrase "a natural substrate of GSK-3" and to recite instead "a known GSK-3 substrate".

As argued hereinabove, claims 1, 2 and 7-9 should be entitled to the benefit of the filing date of parent application 09/951,902 and hence, Applicant believes that the WO Patent Application 01/49709 should not be presented as prior art against claims 1, 2, and 7-9 of the instant application.

In another particular, the Examiner has stated that the effective filing date of claims 5 and 6 is deemed to be January 3, 2001, the filing date of the parent application PCT/US01/00123 (WO 01/49709).

More specifically, the Examiner has stated that claims 5 and 6 are not deemed to be entitled under 35 U.S.C. 119(e) to the benefit of the filing of parent provisional applications 60/174,308 and 60/206,115, because these parent provisional applications, under the test of 35 U.S.C. 112, first paragraph, do not disclose polypeptides in which X can be any amino acid, but rather are limited to polypeptides in which at least one of X is proline.

Claim 1 has now been amended to recite "..., whereas at least one of said X is proline".

Amended claim 1 therefore pertains to polypeptides in which at least one of X is proline and hence teaches the polypeptides disclosed in the parent provisional applications 60/174,308 and 60/206,115. Such polypeptides and their GSK-3 inhibition activity are also widely taught by the parent application PCT/US01/00123 (WO 01/49709), the parent application serial No. 09/951,902, and the instant application (see, for example, Table 1 in Example 1).

Claim 5 of the instant application pertains to a peptide inhibitor that is derived from (patterned after) HSF-1. As is known in the art and is further shown in the instant application (see, for example, Table 1), such polypeptides inherently have at least one proline as the variable X.

Claim 6 recites that this polypeptide has a length of at least 8 amino acid residues.

In the parent provisional applications 60/174,308 and 60/206,115, peptide inhibitors having 7-50 amino acids in length, and preferably 10-13 amino acids in length are disclosed (see, for example, claims 1, 5 and 12 in Provisional Patent Application No. 60/206,115 and claims 1, 4 and 11 in Provisional Patent Application No. 60/174,308).

Applicant therefore believes that claims 5 and 6, which depend from amended independent claim 1, as well as claims 2 and 7-9, should be entitled to the benefit of the filing date of provisional applications 60/174,308 and 60/206,115, namely, January 3, 2000.

In another particular, the Examiner has stated that claims 1, 2 and 7-9 are rejected under 35 U.S.C 102(b) as being anticipated by WO 97/33601. Claim 1 has been amended.

More specifically, the Examiner has stated that WO 97/33601 teaches peptides identified as SEQ ID NOS:6 and 19, which have the same amino acid sequence as recited in claims 1 and 2 of the instant application and peptides identified as SEQ ID NOS:5, 10, 22, 26-31 and 33-38, which have the same amino acid sequence as recited in claims 1, 7 and 8 of the instant application, and that the peptides are combined with pharmaceutically acceptable excipients. The Examiner has continued stating that in view of the similarity in structure between the peptides disclosed in WO 97/33601 and the peptide inhibitors of the claimed invention, the peptides disclosed in WO 97/33601 are deemed inherently capable of inhibiting the enzymatic activity of GSK-3.

WO 97/33601 teaches peptides that are derived from the raf-1 protein and which are designed capable of binding to 14-3-3 protein. More specifically, WO 97/33601 teaches peptides which contain one or more phosphorylated serine residue(s) and have amino acid sequences that are based upon the amino acid residues surrounding two positions of the raf-1 protein, serine-259 and serine-621. This patent application teaches that peptides containing these sequences specifically bind to the 14-3-3 protein, preventing the activation of a protein of the raf-1 family.

WO 97/33601 therefore fails to teach peptides having amino acid sequences that are based upon the amino acid residues surrounding the recognition motif of a GSK-3 substrate.

In sharp distinction, and as is argued hereinabove, the claimed invention is directed at peptides having an amino acid sequence that is part of a GSK-3 substrate, whereby a specific serine residue in the recognition motif of this substrate is replaced by another amino acid residue (denoted as Z, see, claim 1).

Since the peptides taught in WO 97/33601 are based upon an amino acid sequence of a protein that is functionally and structurally unrelated to a GSK-3 substrate, and further since GSK-3 is known as an enzyme with highly specific substrate recognition, it is clear that the peptides disclosed in WO 97/33601 are at least structurally different than the peptides of the claimed invention. It is further clear that the peptides taught in WO 97/33601 are functionally different than the peptides of the claimed invention and hence that the capability of the peptides disclosed in WO 97/33601 to inhibit GSK-3 is implausible.

Notwithstanding the above, and in order to more clearly distinct the claimed invention from the teachings of WO 97/33601, Applicant has chosen to amend claim 1 to recite "..., whereas at least one of said X is proline".

As is well-established in the art (see, for example, "protein kinase resource" in http://www.nih.go.jp/mirror/Kinases/pk_home.html; and Hagit Eldar-Finkelman, TRENDS in Molecular Medicine, Vol. 8, No. 3, pp. 126-132; and Doble and Woodjet, Journal of Cell Science, 116, 1175-1186, which are enclosed herewith) GSK-3, which is an enzyme of the CMG family, is a proline-directed kinase (as are most enzymes in this family). Thus, as is also demonstrated in the instant application (as argued hereinabove), the recognition motif of GSK-3, namely SXXXS(p) includes at least one proline residue, either as one of the Xs therewithin or as a residue at the first position upstream or downstream the recognition motif.

Amended claim 1 therefore reads on peptides that, in addition to the features delineated above, have a proline residue either at the first position downstream the phosphorylated serine residue or at positions 1-5 upstream the phosphorylated serine residue.

None of the peptides disclosed in WO 97/33601 includes a proline residue in these positions.

It is therefore the Applicant's opinion that amended claim 1, as well as claims 2 and 7-9 that directly or indirectly depend therefrom, are not anticipated by WO 97/33601 and are therefore allowable.

Examination of Generic and Non-Elected Claims

In view of the amendments made to the claims and the arguments recited herein it is believed that the claims are allowable with respect to the elected invention.

Applicant wishes to refer to the Examiner's statement in the Restriction Action mailed September 28, 2005, where it is recited as follows:

"Claims 1, 2 and 7-9 link inventions I and II. ..... Upon the allowance of the linking claims, the restriction requirements as to the linked invention shall be withdrawn and any claims depending from or otherwise including all the limitation of the allowable linking claims will be entitled to examination in the instant application".

Hence, examination of claims 1-9 in their generic context and with respect to all the species recited therein is respectfully requested.

In view of the above amendments and remarks it is respectfully submitted that amended claim 1, claims 2-4, amended claim 5, claims 6 and 7, amended claim 8 and claim 9 are now in condition for allowance. Prompt notice of allowance is respectfully and earnestly solicited.

Respectfully submitted,

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Encl.:
Hagit Eldar-Finkelman, TRENDS in Molecular Medicine, Vol. 8, No. 3, pp. 126-132; and
Doble and Woodjet, Journal of Cell Science, 116, 1175-1186